

HYDRAZINE

CAS number: 302-01-2

Synonyms: Diamide, diamine, nitrogen hydrine, hydrazine anhydrous

Chemical formula: N_2H_4

Structural formula: —

Workplace exposure standard (amended)

TWA: 0.01 ppb (0.02 $\mu\text{g}/\text{m}^3$)

STEL: —

Peak limitation: —

Notations: Carc 1B, Sk., DSEN

IDLH: —

Sampling and analysis: The recommended value is likely to be below the current limit of detection for standard sampling and analysis techniques.

Recommendation and basis for workplace exposure standard

A TWA of 0.01 ppb (0.02 $\mu\text{g}/\text{m}^3$) is recommended to protect for the risk of cancer in exposed workers.

Discussion and conclusions

Hydrazine occurs naturally as a product of microbial nitrogen fixation and has been detected in cigarette smoke. It is used as a chemical intermediate, reducing agent, rocket fuel and boiler-water treatment agent.

Hydrazine is carcinogenic in animals through multiple routes of exposure and it is assumed to have carcinogenic potential in humans by some sources. An increased risk of lung cancer is reported in aerospace workers exposed to hydrazine. SCOEL (2016) categorise it as a genotoxic carcinogen. An increased incidence of benign and malignant nasal tumours was observed in rats exposed at 0.05 ppm for one year. ACGIH (2018) classifies its carcinogenicity as of unknown relevance to humans. An increased incidence of pulmonary tumours was reported in a six months mice study at all exposure concentrations ranging from 0.2, 1 or 5 ppm. DFG (1999) did not recommend a MAK due to the potential carcinogenicity risk. Mutagenicity is reported in both *in vitro* and *in vivo* studies. The mechanism of action for carcinogenicity may act *via* a mutagenic mode of action (DFG, 2013; NICNAS, 2014; SCOEL 2016; US EPA, 1987), but is inconclusive. For the purposes of this assessment, hydrazine is assumed to be a non-threshold based genotoxic carcinogen because a genotoxic mechanism of carcinogenicity cannot be ruled out (SCOEL, 2016).

The recommended TWA of 0.01 ppb (0.02 $\mu\text{g}/\text{m}^3$) is derived at a minimal cancer risk level by application of an inhalation slope factor derived from a chronic inhalation study in rats that reported statistically significant increases in nasal tumours. The study was considered adequate, with a sufficient number of animals treated for less than lifetime and observed until death. The study identified a dose-related increase in incidence of tumours (US EPA, 2002).

Recommendation for notations

Classified as a category 1B carcinogen according to the Globally Harmonized System of Classification and Labelling of Chemicals (GHS).

Classified as a skin sensitiser but not a respiratory sensitiser according to the GHS.

A skin notation is recommended based on data in humans and animals of dermal uptake and systemic effects.

DRAFT

APPENDIX

Primary sources with reports

Source	Year set	Standard
SWA	1991	TWA: 0.01 ppm (0.013 mg/m³)
ACGIH	2001	TLV-TWA: 0.01 ppm (0.013 mg/m³)
<p>TLV-TWA recommended to minimise the potential for nasal tumours as observed in rats.</p> <p>Summary of data:</p> <p>Human data:</p> <ul style="list-style-type: none"> • Reports of allergic contact dermatitis • Skin and eye irritation reported • Case report of 6 mo occupational exposure <i>via</i> inhalation and skin (unknown concentration): <ul style="list-style-type: none"> ○ conjunctivitis, tremor, lethargy, lung and liver damage ○ death 21 d after last exposure • Systemic poisoning cases reported effects on the CNS, respiratory system and stomach • 6 cases of vapour inhalation causing pulmonary oedema; no further information • Epidemiological study in 427 workers failed to identify relationship between exposure and cause of death: <ul style="list-style-type: none"> ○ cancer deaths no different than normal ○ a quantitative comparison of rodent carcinogenicity data was applied to this study to predict human cancer risk; predicted that the human incidence of lung cancer would be indistinguishable from the background rate at 1–10 ppm. <p>Animal data:</p> <ul style="list-style-type: none"> • LD₅₀: 93–283 mg/kg (rabbits and guinea pigs, dermal) • Rats, mice, dogs and monkeys continuously exposed at 0.2 or 1 ppm for 6 mo or exposed 6 h/d, 5 d/wk to 1 ppm or 5ppm for 6 mo; effects at 0.2 ppm: <ul style="list-style-type: none"> ○ body weight of rats lower than the controls ○ liver pathology change in mice ○ decrease in the number of RBC in dogs ○ minimal increase in fat deposition in the liver in monkeys • Chronic oral administration to mice; pulmonary adenomas or carcinomas, hepatocarcinomas, myeloid leukaemia, reticulum cell sarcoma of the mediastinum and lymphomas • Chronic oral administration to rats resulted in lung adenomas and carcinomas and in liver tumours • Mice exposed at 0.2, 1 or 5 ppm for 6 mo; increased incidence of pulmonary tumours in all groups • Rats exposed at 0.05 ppm, 1 and 5 ppm 6 h/d, 5 d/wk for 1 yr; followed for their life span or 38 months; increased incidence of benign and malignant nasal tumours; at 0.05 ppm, slight increase incidence of nasal tumours above controls. <p>Genotoxicity:</p> <ul style="list-style-type: none"> • Positive in most standard assays for genetic endpoints • Positive in producing forward mutation in mammalian cells 		

Source	Year set	Standard
<ul style="list-style-type: none"> Produced a point mutation in H-ras gene in cultured newborn rat liver cells Produced reverse mutation in the host-mediated assay in mice. <p>Insufficient data to recommend a sensitiser notation or TLV-STEL.</p>		
DFG	1999	Not assigned
<p>Summary of additional data:</p> <ul style="list-style-type: none"> MAK not assigned due to carcinogenic potential Weakly carcinogenic in rodents Weakly genotoxic even at high dose <i>in vivo</i> or <i>in vitro</i>. 		
SCOEL	2016	Not assigned
<p>Summary of additional data:</p> <ul style="list-style-type: none"> Carcinogenicity is the relevant toxicological endpoint Increased risk of lung cancer in aerospace workers Induced DNA strand breaks in rat hepatocytes and unscheduled DNA synthesis in mouse hepatocyte Induced DNA strand breaks in liver and lungs <i>in vivo</i> in mice Induced the formation of DNA adducts <i>in vitro</i> and of N7-methylguanine and O6-methylguanine in liver of mice, rats and hamsters treated <i>in vivo</i> Mutagenic to yeast and bacteria and induced DNA damage in bacteria Characterised as genotoxic; indirect mechanism of genotoxicity; regarding occupational exposure and respiratory tract effects the existence of a threshold cannot be sufficiently supported. 		
OARS/AIHA	NA	NA
No report.		
HCOTN	NA	NA
No report.		

Secondary source reports relied upon

Source	Year	Additional information
US EPA	✓ 2002	<ul style="list-style-type: none"> Inhalation Unit Risk Factor based on inhalation study in rats; nasal cavity adenoma and adenoma carcinoma A sufficient number of animals treated for less than lifetime and observed until death; a dose-related increase in incidence reported Mutagenicity demonstrated in both <i>in vitro</i> and <i>in vivo</i> Classified as a probable human carcinogen.

Carcinogenicity — non-threshold based genotoxic carcinogens



Is the chemical mutagenic? Yes

Is the chemical carcinogenic with a mutagenic mechanism of action? Yes

The chemical is a non-threshold based genotoxic carcinogen.

Is a cancer slope factor or inhalation unit risk value available? Yes

Inhalation unit risk value ($1/(\mu\text{g}/\text{m}^3)$) 4.9×10^{-3}

Calculated TWA value ($\mu\text{g}/\text{m}^3$) 0.02

Notations

Source	Notations
SWA	Carc. 2
HCIS	Carcinogenicity – category 1B, Skin sensitisation – category 1
NICNAS	Carc. Cat 2
EU Annex	Carcinogenicity – category 1B, Skin sensitisation – category 1
ECHA	Carcinogenicity – category 1B
ACGIH	Carcinogenicity – A3, Skin
DFG	Carcinogenicity – 2, H (skin), Sh (dermal sensitiser)
SCOEL	Carcinogenicity – B, Skin
HCOTN	NA
IARC	Carcinogenicity – Group 2A
US NIOSH	—

NA = not applicable (a recommendation has not been made by this Agency); — = the Agency has assessed available data for this chemical but has not recommended any notations

Skin notation assessment

Calculation

Adverse effects in human case study:	yes
Dermal $\text{LD}_{50} \leq 1000 \text{ mg/kg}$:	yes
Dermal repeat-dose NOAEL $\leq 200 \text{ mg/kg}$:	
Dermal LD_{50} /Inhalation $\text{LD}_{50} < 10$:	
<i>In vivo</i> dermal absorption rate $> 10\%$:	
Estimated dermal exposure at WES $> 10\%$:	

a skin notation is warranted

IDLH

Is there a suitable IDLH value available? No, the chemical is a genotoxic carcinogen

Additional information

Molecular weight:	32.05
Conversion factors at 25°C and 101.3 kPa:	1 ppm = Number mg/m ³ ; 1 mg/m ³ = Number ppm
This chemical is used as a pesticide:	<input type="checkbox"/>
This chemical is a biological product:	<input type="checkbox"/>
This chemical is a by-product of a process:	<input type="checkbox"/>
A biological exposure index has been recommended by these agencies:	<input type="checkbox"/> ACGIH <input checked="" type="checkbox"/> DFG <input type="checkbox"/> SCOEL

Workplace exposure standard history

Year	Standard
Click here to enter year	

References

American Conference of Industrial Hygienists (ACGIH®) (2018) TLVs® and BEIs® with 7th Edition Documentation, CD-ROM, Single User Version. Copyright 2018. Reprinted with permission. See the [TLVs® and BEIs® Guidelines section](#) on the ACGIH website.

Deutsche Forschungsgemeinschaft (DFG) (1999) Hydrazine, hydrazine hydrate and hydrazine salts – MAK value documentation.

EU Scientific Committee on Occupational Exposure Limits (SCOEL) (2016) Recommendation from the Scientific Committee on Occupational Exposure Limits for hydrazine. SCOEL/REC/164.

European Chemicals Agency Regulation (ECHA) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH).

International Agency for Research on Cancer (IARC) (2018) some industrial chemicals. IARC Monographs on the evaluation of the carcinogenic risk to humans.

National Industrial Chemicals Notification and Assessment Scheme (NICNAS) (2018) Hydrazine: Human health tier II assessment – IMAP report.

Tenth Adaptation to Technical Progress Commission Regulation (EU) No 2017/776 amending, for the purposes of its adaptation to technical and scientific progress, Regulation (EC) No 1272/2008 of the European Parliament and of the Council on classification, labelling and packaging of substances and mixtures (the CLP Regulation).

US Environmental Protection Authority (US EPA) (2002) Integrated Risk Information System (IRIS) Chemical Assessment Summary – Hydrazine/Hydrazine sulfate.